Efficacy of phenytoin in the management of ventricular arrhythmias induced by hypokalaemia

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Two cases of ventricular tachycardia and fibrillation induced by hypokalaemia refractory to, or aggravated by, lignocaine and procainamide are recorded. In both instances the administration of phenytoin was associated with an immediate and almost complete suppression of the arrhythmias. Hypokalaemia, procainamide, and quinidine prolong the QT interval and increase temporal dispersion of repolarization. Phenytoin does not increase the QT interval and does not aggravate the underlying disorder in hypokalaemia.

Ventricular arrhythmias induced by hypokalaemia are notorious and often resistant to therapy (Davidson and Surawicz, 1966; Guyer, 1964; Paulley, 1965; Pick, 1966; Sarma, 1965; Scherf, Cohen, and Shafiiha, 1967; Swales, 1964). This phenomenon can be explained by the cellular effects of potassium and some of the more frequently used antiarrhythmic agents. Low potassium (Gettes and Surawicz, 1968), quinidine (Gettes, Surawicz, and Shiue, 1962), and procainamide (Pamintuan, Dreifus, and Watanabe, 1970) prolong the QT interval and thus the vulnerable phase of repolarization (Pick, 1964). Accordingly when both of these agents act synergistically the vulnerable phase is doubly prolonged and may encompass the time of occurrence of premature beats for which the antiarrhythmic agent is being exhibited (Pick, 1964). If the premature beats are not suppressed by the time the vulnerable phase is thus prolonged the likelihood of a repetitive mechanism occurring is greatly enhanced (Palmer, 1962; Watanabe, Dreifus, and Likoff, 1963; Vassalle, 1971). Phenytoin, which has a different mechanism of action at the cellular level and does not prolong the QT interval, would not be expected to have this effect (Palmer, 1962; Watanabe *et al.*, 1963; Gettes, 1971). We recently managed two patients with arrhythmias induced by hypokalaemia where the beneficial effects of phenytoin as compared to the other agents were most striking.

Case reports

Case 1 A 61-year-old alcoholic white woman pre-

sented at the emergency room with a 24-hour history of seizures, hallucinations, and protracted vomiting after a prolonged alcoholic binge. She was conscious, disoriented, and irrational, with cold, clammy skin, a blood pressure of 60 mmHg systolic by palpation, and a pulse of 100 per minute. After examination the patient was placed on a cardiac monitor and shortly thereafter ventricular fibrillation occurred. Direct current countershock reverted the mechanism to sinus rhythm with multiple ventricular premature beats. A 100 mg bolus of lignocaine was given and a lignocaine infusion at 1–2 mg a minute was initiated. The ventricular premature beats persisted with frequent runs of ventricular tachycardia, and after an additional 100 mg of lignocaine the electrocardiogram showed broad, slurred QRS complexes with diffuse TU waves. During the ensuing 25 minutes there were repeated runs of ventricular tachycardia/fibrillation requiring repeated electrical defibrillation (Fig. 1, strips 1 and 2). At this juncture the patient had received a total of 240 mg of lignocaine intravenously without effect, and which indeed had been accompanied by a deterioration in her condition. Due to persistent episodes of ventricular tachycardia and fibrillation the lignocaine infusion was discontinued and phenytoin 250 mg was given intravenously over 5 minutes. During administration of the phenytoin there was one further episode of ventricular flutter, corrected by direct current countershock (Fig. 1, strip 2) (400 joules). Sinus rhythm was maintained thereafter for 15 minutes when a further episode of ventricular fibrillation occurred responding to a single countershock. An additional 100 mg of phenytoin was administered intravenously stabilizing the rhythm without further ventricular premature beats or ventricular tachycardia (Fig. 1, strip 3). At this time biochemical evaluation revealed pH of 7·5 and K^+ of only 2·2 mEq/l. An infusion of KCl at 20 mEq per hour was started, with an additional 1 mEq KCl directly over 5 minutes – some time after the first dose of phenytoin. In an effort to improve the haemodynamics and further stabilize the
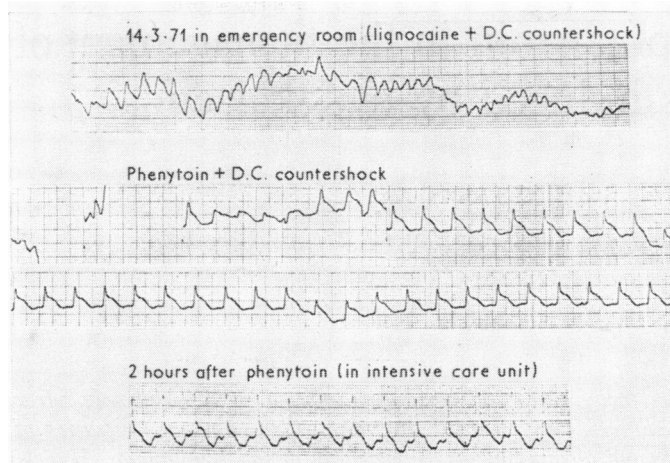
FIG. I   *Case 1. Representative electrocardiogram strips – details in text.*

myocardial electrical activity an isoprenaline infusion at 3 µg per minute was initiated, and continued for 12 hours at 1 µg per minute with apparently good effect. KCl was also continued intravenously. A further 150 mg of phenytoin was given intravenously 140 minutes after the initial arrest making a total of 500 mg over 75 minutes. Cardiac rhythm remained stable and the QRS complex became narrower (Fig. 1, strip 4). Phenytoin was continued for four days. During this time the patient's electrolytes and calcium slowly returned to normal, magnesium initially at 1·18 mg/100 ml was replaced with magnesium sulphate 50 per cent solution 10 ml intramuscularly, twice a day. Urine output was good. The blood pressure rose to 120/70 mmHg, and though she remained drowsy with poor air exchange for some days she eventually recovered.

Case 2   A 60-year-old white woman presented in atrial fibrillation with a ventricular response of 115 per minute and ectopic ventricular contractions, congestive heart failure, and respiratory insufficiency. She was transferred to the medical intensive care unit. Digoxin 25 mg intravenously, frusemide 120 mg intravenously, and a slow infusion of aminophylline (0·5 g/l.) was administered, with, in addition, lignocaine 1 mg per minute for the ventricular premature beats. Her P_aO_2 remained low and she continued to deteriorate, requiring intubation and assisted ventilation. Initially the ventricular premature beats were suppressed by the lignocaine infusion, but after 36 hours resistant multifocal ventricular premature beats developed (Fig. 2, strip 1). Procainamide 250 mg intramuscularly and 100 mg intravenous bolus of phenytoin were given with initially brief suppression of the arrhythmias. Procainamide was continued at 500 mg every 6 hours intramuscularly, without effect, the ventricular premature beats becoming more frequent. After a total of 1·25 g procainamide a brief episode of ventricular tachycardia occurred (Fig. 2, strip 2)

aborted by lignocaine 100 mg. The multifocal ventricular premature beats persisted with runs of ventricular tachycardia. Procainamide was discontinued, and as lignocaine 100 mg was ineffective phenytoin 300 mg was administered over 8 minutes. The rhythm stabilized without further episodes of ventricular tachycardia and only occasional ventricular premature beats. Biochemical evaluation later showed an arterial pH of 7·66, Po_2 61 mmHg (on 60% oxygen via ventilator), and a potassium 2·6 mEq/l. An intravenous infusion of KCl at 10 mEq/hr was initiated. The rhythm remained stable for 14 hours (Fig. 2, Strip 3) – phenytoin 100 mg intravenously every 3 hours was continued for 48 hours. Subsequently the rhythm remained stable with only occasional ventricular
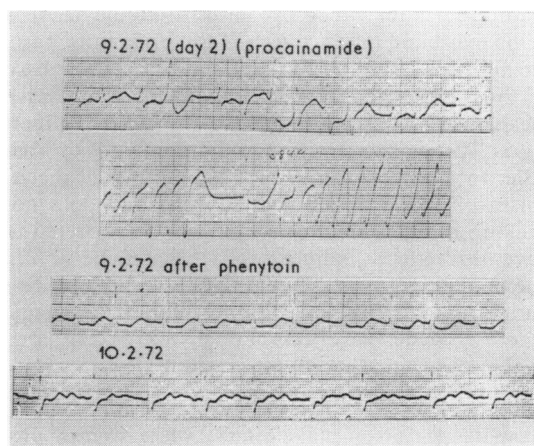

FIG. 2   *Case 2. Representative electrocardiogram strips – details in text.*

premature beats. Thereafter the patient followed a fairly stable course with return of blood chemistries to normal.

Discussion

The effectiveness of phenytoin in suppressing ventricular arrhythmias is well established (Damato, 1969; Mercer and Osborne, 1967; Rosen, Lisak, and Ruben, 1967). Those occurring during anaesthesia, after cardioversion, and associated with digitalis intoxication are particularly responsive (Helfant, Scherlag, and Damato, 1967; Bashour *et al.*, 1968). Eddy and Singh (1969) successfully abolished ventricular fibrillation previously unresponsive to intracardiac procainamide, propranolol, and direct current countershock in a 14-year-old girl after cardiac surgery with phenytoin; while Osborne (1964) suggested that phenytoin should be part of the routine drug armamentarium for the management of circulatory arrest. Despite this, little emphasis has appeared in the published reports on the effectiveness of phenytoin in the presence of hypokalaemia. This is the more remarkable as both procainamide and quinidine prolong the QT interval and so must aggravate the underlying defect which predisposes to arrhythmias when the serum potassium is low (Gettes *et al.*, 1962; Gettes and Surawicz, 1968; Pamintuan *et al.*, 1970). Phenytoin, which has a different action at the cellular level and does not prolong the QT interval, seems an obvious choice in such a case (Pamintuan *et al.*, 1970; Watanabe *et al.*, 1963; Gettes, 1971).

Although both patients received potassium, which by itself may suppress arrhythmias (Reynolds, 1965), this was not the mechanism of suppressing the arrhythmias (at least initially) in these two instances. The beneficial response occurred within 5 minutes of the administration of phenytoin in situations where lignocaine and procainamide had been ineffective. Rosen *et al.* (1967) had similar experiences with phenytoin in patients with hypokalaemia. This ability of phenytoin to suppress refractory ventricular arrhythmias in the presence of hypokalaemia and multiple electrolyte deficiencies is a valuable property, especially as the usual first line drug, lignocaine, is frequently ineffective in this setting (Vassalle, 1971).

Although phenytoin reduces sodium conductance in brain cells, it is not thought to have an identical effect on the myocardium. It does not prolong the repolarization process; on the contrary it tends to shorten the action potential and possibly enhance phase 4 prepotential (Gettes and Surawicz, 1968; Gettes, 1971; Pamintuan *et al.*, 1970). The shorter duration action potential and therefore relatively shortened refractory period will help prevent disorganization of the excitation front (Helfant *et al.*,

1967; Pamintuan *et al.*, 1970; Gettes, 1971). This will alleviate the underlying electrical defect which initially facilitated the repetitive mechanism by producing temporal dispersion of repolarization (Han *et al.*, 1966; Han, 1971; Vassalle, 1971). As the QT interval and therefore the vulnerable phase is not prolonged into the period of occurrence of premature beats, even if the latter are not fully suppressed they will not tend to produce a repetitive mechanism (Palmer, 1962; Pick, 1964) – as can occur with the administration of quinidine (Gettes *et al.*, 1962) and procainamide (Pamintuan *et al.*, 1970).

As phenytoin is probably taken up by the fat depots, an initial loading dose of 3–5 mg/kg may be required. This must be given slowly at a maximum rate of 50 mg per minute (Damato, 1969). In the nonemergent situation the dose schedule suggested by Bigger, Schmidt, and Kutt (1968) may be used, consisting of increments of 100 mg given at 5-minute intervals until the arrhythmia is abolished, until 1 g has been given, or until undesirable side effects appear. Constant monitoring of electrocardiogram is essential during this procedure.

Phenytoin is generally considered to be safe (Rosen *et al.*, 1967; Damato, 1969), side effects being generally mild unless administration is too rapid, when bradycardia, hypotension, and transient atrioventricular block may occur (Karliner, 1967). Long-term side effects such as drowsiness, giddiness, and nystagmus are usually not experienced during the treatment of cardiac arrhythmias.

In closing we would like to emphasize the usefulness of phenytoin in the management of the notoriously resistant and malignant arrhythmias associated with hypokalaemia, where the usual antiarrhythmic agents are at the best ineffective and may even be dangerous. Indeed when hypokalaemia is suspected, phenytoin should probably be the initial drug of choice.

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